REMARKS

Claims 1, 2, 4-10, 22-25, 28, and 31 have been amended and new claims 32-44 have been added. Claims 3, 11-21, 26, 27, 29, and 30 have been canceled without prejudice or disclaimer. Claims 1, 2, 4-10, 22-25, 28, and 31-44 are pending in the instant application. Support for the amendments to the claims can be found in the specification at, for example, page 19, lines 22-27; page 20, lines 22-24; page 20, lines 25-30; page 21, line 31 to page 22, line 9; page 22, lines 16-20; and page 25, lines 9-19; and in Table I (pages 25-26). No new matter has been added as a result of the above-described amendments. The rejections set forth in the Office Action have been overcome by amendment or are traversed by argument below.

1. Claim of priority

The Office Action asserts that Applicants have not complied with one or more conditions for receiving the benefit of one or more prior filed copending nonprovisional applications, international applications designating the United States of America, or provisional applications. The Action states that the instant specification must be amended to contain a reference to each such prior application in the first sentence following the title, identifying each application by application number, or international application number and international filing date, indicating the relationship of the applications, and if the benefit of an international application is claimed, indicating whether the international application was published under PCT Article 21(2) in English.

Applicants have amended the first sentence of the specification so that it contains a reference to each prior nonprovisional, provisional, and International application for which the benefit of priority has been claimed.

2. Objections to claims 2, 4-12, 22, 24, 25, 28, and 31

The Office Action contains an objection to claims 2 and 4-12 because the term "factor" is missing after the term "tumor necrosis." Applicants have amended claims 2, 4-12, and 22 to recite a tumor necrosis factor binding protein.

The Action also contains an objection to claims 4-12, 22, 24, 25, 28, and 31 as depending from a claim encompassing a non-elected invention. Applicants have amended claims 4-8, 11, 12, 22-25, 28, and 31 so that these claims only depend from pending claims encompassing the elected

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invention.

The Action also contains an objection to claims 6-8, 11, 12, 23, 28, and 31 under 37 C.F.R. § 1.75(c) as being of improper dependent form because a multiple dependent claim cannot depend from any other multiple dependent claim. Applicants have amended claims 6-8, 11, 12, 23, 28, and 31 so that no multiple dependent claim depends either directly or indirectly from another multiple dependent claim.

The Action also contains an objection to claim 10 under 37 C.F.R. § 1.821(d) as describing a sequence that is set forth in the Sequence Listing without making reference to the sequence by the use of a sequence identifier. Applicants have amended claim 10 so that the amino acid sequence constituents of the recited polyvalent tumor necrosis factor binding protein are described using sequence identifiers.

The Action contains an objection to claims 11 and 12 under 37 C.F.R. § 1.75(c) as being in improper dependent form for failing to further limit the subject matter of a previous claim. Applicants have canceled claims 11 and 12 without prejudice or disclaimer, rendering this objection moot.

Applicants submit that the objections to the claims have been overcome by amendment, and therefore, respectfully request that these objections be withdrawn.

3. Rejection of claims 2, 4, and 5 under 35 U.S.C. § 101

The Office Action asserts a rejection of claims 2, 4, and 5 under 35 U.S.C. § 101. The Action states that because the naturally occurring non-isolated full-length TNFR-I or naturally occurring soluble form of TNFR-I comprise polypeptides that are variants of the proteins of SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, the claimed invention is directed to non-statutory subject matter.

As helpfully suggested by the Examiner in the instant Office Action, Applicants have amended claim 2 to recite "[a]n isolated tumor necrosis factor binding protein." Applicants contend that claim 2, as amended, is clearly not directed to non-statutory subject matter, and therefore, respectfully request that the rejection of claim 2 under 35 U.S.C. § 101 be withdrawn.

4. Rejections of claims 1, 2, 4-12, 22-25, 28, and 31 under 35 U.S.C. § 112, first paragraph

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The Office Action asserts a rejection of claims 1, 2, 4-12, 22-25, 28, and 31 under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Action acknowledges that the specification teaches the extracellular domain of human Tumor Necrosis Factor Receptor-1 (*i.e.*, SEQ ID NO: 2), which comprises four cysteine rich domains, and teaches truncation variants of sTNFR-I. The Action also recognizes that while the prior art disclosed that truncated sTNFR-I proteins lacking the first, second, or third cysteine rich domains could *not* bind TNF, the instant specification teaches truncated sTNFR-I proteins lacking a portion of the third domain, and optionally a portion of the first domain, that do indeed bind TNF. The Action asserts, however, that the disclosure of a single polypeptide (SEQ ID NO: 2), and of several truncation variants of that polypeptide (SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, and SEQ ID NO: 14), does not adequately support the scope of the claimed genus, which the Office views as encompassing polypeptides that vary substantially in length and amino acid composition. The Action also asserts that while the specification includes in the "variants" of the invention, allelic variants and insertion, deletion, and substitution variants, the specification does not explicitly disclose allelic variants of SEQ ID NO: 2, and the only insertion, deletion, or substitution variants are those of SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, and SEQ ID NO: 14, which either have an additional methionine residue at their amino terminal end or a single amino acid substitution at their carboxyl terminus.

Applicants note that the specification defines sTNFR-I "variants" as including naturally-occurring allelic variants, deletion variants, addition variants, and substitution variants (page 19, lines 11-21). Applicants also note that the specification defines "deletion variants" as including amino-terminal, carboxyl-terminal, and internal intrasequence deletions (page 19, lines 26-27), and that the specification defines "addition variants" as including amino-terminal, carboxyl-terminal, and internal intrasequence insertions (page 20, lines 22-26). Applicants have amended claim 1 to recite: (a) particular truncated sTNFR-I polypeptides; (b) polypeptide variants of (a) having at least one amino acid substitution; (c) polypeptide variants of (a) having at least one amino acid addition; and (d) polypeptide variants of (a) having at least one internal intrasequence amino acid deletion. Applicants have amended claim 2 to recite: (a) particular truncated sTNFR-I polypeptides; (b)

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polypeptide variants of (a) having at least one amino acid substitution; (c) polypeptide variants of (a) having at least one amino acid addition, provided that the polypeptide variant does not comprise amino acid residues 111-161 of SEQ ID NO: 2 or a portion thereof; and (d) polypeptide variants of (a) having at least one internal intrasequence amino acid deletion. Applicants contend that amended claims 1 and 2 do not define a genus of truncated sTNFR-I polypeptides that vary substantially in length and amino acid composition, as these claims no longer recite all "variants and derivatives" of the truncated sTNFR-I molecules of the invention, and therefore, no longer encompass truncated sTNFR-I variants having amino-terminal and/or carboxyl-terminal deletions (*i.e.*, truncated sTNFR-I variants having additional truncations) or naturally-occurring sTNFR-I allelic variants.

In addition, Applicants note that the specification teaches that deletions may be made in the regions of the described truncated sTNFR-I polypeptides sharing a low degree of homology with the amino acid sequences of other cell surface membrane proteins in the NGF/TNF receptor family (page 20, lines 1-5). The specification also teaches that the sequence similarity among NGF/TNF receptor family members is particularly high in the regions corresponding to the first two disulfide loops of domain 1, the whole of domain 2, and the first disulfide loop of domain 3 (page 20, lines 10-14), and describes two exemplary truncated sTNFR-I deletion variants (*i.e.*, sTNFR-I-ΔThr^{20} and sTNFR-I-ΔCys^{19}; page 20, lines 16-17). Applicants also note that the specification teaches that one of ordinary skill in the art would understand the positions in the described truncated sTNFR-I polypeptides that would be tolerable of amino acid substitution by reference to similar or identical residues in related proteins (page 23, lines 25-29). The specification also teaches that one of ordinary skill in the art would appreciate that truncated sTNFR-I substitution variants could be determined using information previously elucidated regarding the full length sTNFR-I and sTNFR-II molecules (page 24, lines 4-7). For example, the specification teaches that (a) residues Tyr^{9}, Thr^{39}, His^{55} in Domain 1, residues Phe^{49}, Ser^{63}, Asp^{82} in Domain 2 and residues Tyr^{92} and Ser^{107} in Domain 3 are important for the stabilization of the structure of Domains 1, 2 and 3, respectively; (b) residues Pro^{12} and His^{55} interact with Ser^{86}-Tyr^{87} on subunit C of TNFα; (c) residues Glu^{45}-Phe^{49} are in a loop that interacts with residues Leu^{29}-Arg^{32} of TNFα subunit A; (d) residue Gly^{48} interact with Asn^{19}-Pro^{20} on subunit A of TNFα; (e) residues His^{58}-Leu^{60} are in an extended strand conformation and have side chain interactions with residues Arg^{31}-Ala^{33} on subunit A of TNFα; (f) residue His^{58}

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interacts with residue Arg^{31} on subunit A of TNFα; (g) residues Lys^{64}-Arg^{66} are in an extended strand conformation and have side chain and main chain interactions with residues Ala^{145}-Glu^{146} and residue Glu^{46} on subunit A of TNFα; (h) residue Met^{69} interacts with residue Tyr^{115} on subunit A of TNFα; (i) residues His^{94}-Phe^{101} form a loop that interacts with residues Thr^{73}-Leu^{75} and Asn^{137} of subunit C of TNFα; (j) residue Trp^{96} of sTNFR-I interacts with residues Ser^{71}-Thr^{72} on subunit C of TNFα; (k) residue Leu^{100} of sTNFR-I is in close proximity to residue Asn^{137} on subunit C of TNFα; and (l) residue Gln^{102} of sTNFR-I interacts with residue Pro^{113} on subunit A of TNFα (page 24, line 10 to page 25, line 9). The specification also teaches rubrics recognized in the art for conservative amino acid substitutions (page 26, line 2 to page 28, line 6 and Table I, pages 25-26).

In view of the teachings in the specification and knowledge in the art at the time the instant application was filed, Applicants contend that one of ordinary skill in the art would understand the scope of species comprising the genus of truncated sTNFR-I variants defined by claims 1 and 2, and that the inventors were in possession of the invention having said scope at the time the application was filed. Applicants, therefore, submit that claims 1 and 2, as amended, satisfy the written description requirement of 35 U.S.C. § 112, first paragraph, and respectfully request that this ground of rejection be withdrawn.

The Office Action also asserts a rejection of claims 1, 2, 4-12, 22-25, 28, and 31 under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention. The Action acknowledges that the specification is enabling for the polypeptide of SEQ ID NO: 2 and for truncation variants of the polypeptide of SEQ ID NO: 2; however, the Action asserts that the specification does not reasonably provide enablement for variants of these polypeptides. Specifically, the Action states that one of ordinary skill in the art could not make a protein comprising an amino acid sequence having a TNF core binding sequence other than the one disclosed in the specification and expect it to bind TNF. The Action also states that because the specification does not identify those residues in the amino acid sequences of explicitly-disclosed SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, and SEQ ID NO: 14 that are essential for the biological activity of these sequences, a person skilled in the art would have to resort to undue experimentation to make and use the claimed invention throughout its full scope, in the form of insertional, deletional, and substitutional

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mutation analysis ofTNF binding protein variants.

As described above, Applicants have amended claims 1 and 2 so that they no longer recite truncated sTNFR-I variants and derivatives, and therefore, no longer encompass truncated sTNFR-I variants having amino-terminal and/or carboxyl-terminal deletions (*i.e.*, truncated sTNFR-I variants having additional truncations), truncated sTNFR-I variants having amino-terminal and/or carboxyl-terminal insertions (*i.e.*, truncated sTNFR-I variants in which one or more amino acid residues is added, resulting in the reconstruction of sTNR-I), and naturally-occurring sTNFR-I allelic variants. Applicants contend that the explicit teachings described above, combined with knowledge well-known in the art, would permit one of ordinary skill in the art to make and use the claimed invention throughout its full scope without the exercise of undue experimentation.

Applicants also respectfully disagree with the Action's assertion that the claims of the instant application are analogous to claim 7 of U.S. Patent No. 4,703,008 (the '008 patent), which was held invalid for lack of enablement in *Amgen Inc. v. Chugai Pharmaceuticals Co.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991). In that case, the Federal Circuit did not set forth a *per se* rule that claims to substitution and other variants of disclosed nucleotide or amino acid sequences were inherently invalid or required explicit support for each and every claimed species. Rather, the Court noted that for inventions directed to DNA sequences, the specification must disclose how to make and use enough sequences to justify the grant of the claims sought in order to enable one skilled in the art to carry out the invention commensurate with the scope of the claims. *Amgen Inc.*, 927 F.2d at 1213. The Court determined that the specification of the '008 patent was insufficient to enable one of ordinary skill in the art to make and use the claimed invention because it disclosed how to make and use only a few of the *nearly infinite* number of erythropoietin variants encompassed by claim 7 and little or no information on structural features of the EPO molecule important for red blood cell producing activity (in addition, the trial court had found that a skilled artisan, by making substitutions at only three positions in the erythropoietin sequence, could generate over a million different erythropoietin variants). *Id.* Because the disclosure was limited to only a few explicitly-recited erythropoietin variants, the specification failed to disclose how to make and use enough sequences to justify a claim encompassing *all* DNA sequences that encode a polypeptide having erythropoietin-like activity. *Amgen Inc.*, 927 F.2d at 1213-14.

In stark contrast, the instant application teaches, *inter alia*, that truncated sTNFR-I proteins

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lacking a portion of the third domain, and optionally a portion of the first domain, bind TNF (in contrast to the prior art, which disclosed that truncated sTNFR-I proteins lacking the first, second, or third cysteine rich domains could not bind TNF); that the sequence similarity among NGF/TNF receptor family members is particularly high in the regions corresponding to the first two disulfide loops of domain 1, the whole of domain 2, and the first disulfide loop of domain 3; two exemplary truncated sTNFR-I deletion variants; numerous residues important to the biological function of sTNFR-I and sTNFR-II; and a list of exemplary conservative substitutions. Applicants respectfully contend that because the specification discloses how to make and use enough sequences to enable one skilled in the art to carry out the invention commensurate with the scope of the claims, the claims of the instant application are not analogous to claim 7 of the '008 patent. Applicants, therefore, submit that claims 1 and 2, as amended, satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, and respectfully request that this ground of rejection be withdrawn.

Applicants respectfully contend that rejections based on 35 U.S.C. § 112, first paragraph, have been overcome by amendment or traversed by argument, and request that the Examiner withdraw all rejections made on this basis.

5. Rejections of claims 1, 2, 4-12, 22-25, 28, and 31 under 35 U.S.C. § 112, second paragraph

The Office Action asserts a rejection of claims 1, 2, 4-12, 22-25, 28, and 31 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. The Action states that although the specification discusses sTNFR-I derivatives, claims 1 and 2 are indefinite for reciting the term "derivative" because the metes and bounds of a "derivative" are not defined.

Applicants have amended claims 1 and 2 to delete the term "derivative." Applicants contend that claims 1 and 2, as amended, satisfy the definiteness requirement of § 112, second paragraph, and therefore, respectfully request that this ground of rejection be withdrawn.

5. Rejection of claim 2 under 35 U.S.C. § 102

The Office Action asserts a rejection of claim 2 under 35 U.S.C. § 102(b), as being anticipated by International Publication No. WO 92/16221 (Thompson *et al.*). The Action states that

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Thompson *et al.* disclose a 30 kDa TNF binding protein that is 100% identical to the polypeptide of SEQ ID NO: 2. The Action also states that because the specification describes truncated sTNFR-I variants as including the polypeptides of SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, and SEQ ID NO: 14 with deleted, inserted, or substituted amino acid residues, the 30 kDa TNF binding protein disclosed by Thompson *et al.* comprises a truncated sTNFR-I variant, and therefore, anticipates claim 2.

As described in section 4 above, Applicants have amended claim 2 to include the proviso that the polypeptide does not include amino acids 111-161 of SEQ ID NO: 2. This same language is found in Claim 1, which was not subject to a rejection under § 102. Thus, claim 2, as amended, no longer encompasses a reconstructed sTNFR-I protein (*i.e.*, the 30 kDa TNF binding protein disclosed by Thompson *et al.*). Because Thompson *et al.* does not disclose a protein that meets each and every limitation of the claimed invention, Thompson *et al.* cannot anticipate claim 2, as amended. Applicants, therefore, respectfully request that the rejection of claim 2 under 35 U.S.C. § 102(b) be withdrawn.

CONCLUSIONS

Applicants respectfully contend that all conditions of patentability are met in the pending claims as amended. Allowance of the claims is thereby respectfully solicited.

If Examiner O'Hara believes it to be helpful, she is invited to contact the undersigned representative by telephone at 312-913-0001.

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